REMARKS

Status Summary

The United States Patent and Trademark Office (hereinafter the "Patent Office") has examined claims 1-40, as presented in the present U.S. patent application, which was filed on September 11, 2003. The Patent Office has issued a non-final first Official Action. As set forth in the Official Action, claims 1-40 are rejected.

Claim 36 is objected to for a typographical error. Specifically, it is asserted that the sentence segment "...comprises. a formulation..." is not supposed to contain a period. Applicants respectfully submit that the appropriate correction has been made.

Claims 1, 4, 6, 7, 19, 20, and 25-28 stand rejected by the Patent Office under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by PCT Published Application No. WO98/44910 to Lang, hereinafter referred to "Lang". Claims 8, 12, 13, 15-18, 22, 23, 29-31, 33 and 34 are rejected under 35 U.S.C. 103(a) upon the contention that the claims are unpatentable over Lang in view of U.S. Patent No. 5,810,888 to Fenn (hereinafter "Fenn"). Claims 2, 3, 9-11, 35 and 37-40 are rejected under 35 U.S.C. 103(a) upon the contention that the claims are unpatentable over Lang in view of Fenn and further in view of U.S. Patent No. 5,149,319 to Unger (hereinafter "Unger '319"). Claims 14, 24, 32 and 36 are rejected under 35 U.S.C. 103(a) upon the contention that the claims are unpatentable over Lang in view of Fenn, further in view of Unger '319 and further in view of U.S. Patent

No. 5,542,935 to Unger et al. (hereinafter "Unger et al. '935"). Claims 5 and 21 are rejected under 35 U.S.C. 103(a) upon the contention that the claims are unpatentable over Lang in view of U.S. Patent No. 4,728,575 to Gamble et al. (hereinafter "Gamble et al.").

Claims 1, 3 and 11 have been amended to more particularly point out and distinctly claim the presently disclosed subject matter. Claim 2 has been cancelled. Support for the amendments can be found throughout the application as filed. See for example, page 27, lines 3-14, and page 30, lines 17-23 of the present U.S. patent application. New claims 41-46 have been added. Support for the new claims can be found at page 42, lines 24-33, and page 43, lines 1-2 of the present U.S. patent application. No new matter has been added. Thus, upon submission of this amendment, claims 1 and 3-46 are pending in the present application.

Response to the Rejection of Claims Under 35 U.S.C. § 102(b)

Based on Lang

Claims 1, 4, 6, 7, 19, 20, and 25-28 stand rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Lang. The Patent Office asserts that Lang discloses a method comprising identical active steps of the subject invention as claimed. More specifically, the Patent Office asserts that Lang discloses a method of monitoring drug delivery to a tumor, comprising administering a non-sensitive liposome composition, wherein the liposome encapsulates a contrast agent and a therapeutic agent, and monitoring the accumulation of the compound of

interest at the tumor site using MRI. The positions of the Patent Office as summarized above with respect to claims 1, 4, 6, 7, 19, 20, and 25-28 are respectfully traversed as described below.

Claim 1 has been amended to clarify the claimed subject matter. Specifically, claim 1 has been amended to recite a method of monitoring the accumulation of a compound of interest at a desired site *in vivo* by MRI, the method comprising administering to a subject a non-sensitive liposome composition, and monitoring the accumulation of the compound of interest at the desired site, wherein there is increased blood flow to the desired site. Referring to the specification, for example, blood flow can be increased to a desired site by a variety of techniques and/or as a result of a natural process. See page 12, lines 10-12, and page 27, lines 3-14, of the present U.S. patent application. Further, an increase of blood flow to a desired site can result in both thermosensitive and non-sensitive liposomes selectively collecting at the desired site. See page 30, lines 17-23, of the present U.S. patent application.

Applicants respectfully submit that Lang does not disclose a method of monitoring the accumulation of a compound of interest at a desired site *in vivo* by MRI, wherein there is increased blood flow to the desired site. Thus, applicants respectfully submit that Lang does not teach each and every element of claim 1. Because claims 4, 6 and 7 depend from claim 1 and therefore share the novel features of claim 1 described above, applicants respectfully submit that claims 4, 6 and 7 are also patentably distinguished over Lang. Allowance of the claims is respectfully requested.

With respect to claims 19, 20 and 25-28, applicants respectfully submit that Lang does not teach, or even mention, a method of detecting an *in vivo* blood pool. Specifically, Lang does not teach a method to detect an *in vivo* blood pool by administering a liposome composition to a subject, generating a magnetic resonance image and detecting the presence of an *in vivo* blood pool by analyzing the magnetic resonance image.

Thus, applicants respectfully submit that claims 1, 4, 6, 7, 19, 20 and 25-28 are patentably distinguished over Lang. Allowance of claims 1, 4, 6, 7, 19, 20 and 25-28 is respectfully requested.

Response to the Rejection of Claims Under 35 U.S.C. § 103(a)

Based on Lang in View of Fenn

Claims 8, 12, 13, 15-18, 22, 23, 29-31, 33 and 34 stand rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lang in view of Fenn. As described above, the Patent Office asserts that Lang discloses a method of monitoring drug delivery to a tumor, comprising administering a non-sensitive liposome composition, wherein the liposome encapsulates a contrast agent and a therapeutic agent, and monitoring the accumulation of the compound of interest at the tumor site by MRI. The Patent Office admits that the reference lacks particular disclosure about the use of a thermosensitive liposome. However, the Patent Office contends that the teachings of the Fenn compensate for this deficiency.

According to the contentions of the Patent Office, Fenn teaches the use of a thermosensitive liposome for drug delivery by transmitting electromagnetic radiation to the site of interest wherein the liposome contains chemotherapy agents. The Patent Office also contends that Fenn discloses the possibility of using medical imaging modalities such as MRI to detect the temperature of the site while heating. Therefore, the Patent Office contends that it would have been *prima facie* obvious to one of ordinary skill in the art to modify Lang to include the use of a thermosensitive liposome in the method of drug delivery and monitoring as evidenced by Fenn. The positions of the Patent Office as summarized above with respect to claims 8, 12, 13, 15-18, 22, 23, 29-31, 33 and 34 are respectfully traversed as described below.

Applicants respectfully submit that the aforementioned discussion regarding the deficiencies of the methods disclosed by Lang is maintained in response to the current rejection.

Regarding claims 8, 12, 13 and 15-18, applicants respectfully submit that neither Lang nor Fenn, alone or in combination, teach or suggests methods of monitoring the localization and distribution of a compound of interest to a desired site utilizing an envirosensitive liposome. Specifically, the proposed combination of Lang and Fenn does not disclose a method of monitoring drug distribution (including drug release) from an envirosensitive liposome using MRI. See, for example, page 30, lines 8-15. Lang does not disclose an envirosensitive liposome nor demonstrate the ability to monitor drug distribution (including drug release) from a liposome. Fenn fails to teach or suggest that MRI coupled with a contrast agent could be used to

monitor drug distribution (including drug release) from the envirosensitive liposome at the desired site. Rather, Fenn is at best generally interested in a method to heat a specific site using a thermodynamically adaptive phased array system to activate thermosensitive liposomes. Accordingly, the combined teachings of Lang and Fenn do not provide a method to monitor or quantify drug distribution (including drug release) at the desired site, and thus, at best, they assume liposome drug release.

Additionally, regarding claims 8, 12, 13, 15-18, 29-31, 33 and 34, the proposed combination of Lang and Fenn does not teach or suggest an *in vivo* method of monitoring the localization and distribution or the accumulation of a compound of interest, wherein the monitoring is performed as the compound of interest is being released from the envirosensitive liposome at the desired site. The presently disclosed envirosensitive liposomes can provide contrast enhancement, even at temperatures below their transition temperatures, as compared to non-envirosensitive liposomes. See Figures 1C and 1D of the instant U.S. patent application as filed. Also, as disclosed in the instant specification, the monitoring of the accumulating or localization and distribution of the compound of interest can be accomplished in less than five minutes (see, for example, page 42, lines 24-30) and as little as 1 minute 45 seconds (see, for example, page 49, lines 18-19).

In marked contrast, the methods disclosed by Lang require substantially longer time periods for the monitoring disclosed therein. For example, tumor enhancement 5 minutes after Gd-labeled liposomes were injected provided only minimal enhancement of tumor tissue and tumor tissue enhancement, not believed to

be statistically different from a pre-contrast image, and did not reach a maximum until 24 hours post injection. See page 12, lines 10-20, and Figure 1, of Lang. Accordingly, pre- and postcontrast images would be obtained with a time separation of 24 hours and thus could not be done within a single imaging session. See page 18, lines 3-5, of Lang. Additionally, Fenn does not compensate for this deficiency in Lang.

Therefore, applicants respectfully submit that it would not have been *prima facie* obvious to a skilled artisan at the time of the invention to combine the teachings of Lang and Fenn to provide a method of monitoring the localization and distribution or accumulation of a compound of interest in accordance with the presently claimed subject matter. Further, there would have been no reasonable expectation of success in combining the teachings of Lang and Fenn to provide methods in accordance with the presently claimed subject matter.

Finally, applicants respectfully submit that the combined teachings of Lang and Fenn do not teach each and every element of claims 8, 12, 13, 15-18, 29-31, 33 and 34. As such, applicants respectfully submit that claims 8, 12, 13, 15-18, 29-31, 33 and 34 are distinguished over the combination of Lang and Fenn.

Claims 22 and 23 are dependent from claim 19 and pertain to detection of an *in vivo* blood pool is detected. Applicants respectfully submit that Fenn does not teach a method of detecting a blood pool *in vivo* in accordance with the presently claimed subject matter. Thus, Fenn does not compensate for the deficiencies of Lang, as noted above.

Thus, applicants respectfully submit that the teachings of Fenn do not compensate for the deficiencies of Lang. Applicants respectfully request that the rejection of claims 8, 12, 13, 15-18, 22, 23, 29-31, 33 and 34 under 35 U.S.C. 103(a) be withdrawn. Applicants also respectfully request that the claims be allowed.

Response to the Rejection of Claims Under 35 U.S.C. § 103(a)

Based on Lang in View of Fenn and Further in View of Unger '319

Claims 2, 3, 9-11, 35 and 37-40 stand rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lang in view of Fenn and further in view of Unger '319. As described above, the Patent Office asserts that Lang discloses a method of monitoring drug delivery to a tumor, comprising administering a non-sensitive liposome composition, wherein the liposome encapsulates a contrast agent and a therapeutic agent, and monitoring the accumulation of the compound of interest at the tumor site by MRI. Further, the Patent Office contends that Fenn teaches the use of a thermosensitive liposome. The Patent Office admits that neither Lang nor Fenn, alone or in combination, teaches the use of ultrasound to heat the tumor site. However, the Patent Office contends that the teachings of Unger '319 compensate for this deficiency.

According to the contentions of the Patent Office Unger '319 teaches the use of ultrasound to heat the tumor site. Therefore, the Patent Office contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Unger '319 with that of

Lang. The positions of the Patent Office as summarized above with respect to claims 2, 3, 9-11, 35 and 37-40 are respectfully traversed as described below.

Applicants respectfully submit that claim 2 has been cancelled, thus mooting the rejection of this claim.

Applicants respectfully submit that the aforementioned discussion regarding the deficiencies of the methods disclosed by Lang and Fenn in monitoring the accumulation and distribution of a compound of interest *in vivo* is maintained in response to the current rejection.

Applicants respectfully submit that Unger '319 does not compensate for the deficiencies of Lang and/or Fenn. Rather, Unger '319 at best teaches a method of heat treating biological tissues and fluids using a hyperthermic potentiator in combination with ultrasound. Accordingly, the ultrasound heating taught by Unger '319, wherein the hyperthermic treatment of tumors is enhanced by coupling hyperthermic potentiators and ultrasound, is not tantamount to using ultrasound to heat a desired site *in vivo* such that the accumulation and distribution of a liposome encapsulated compound of interest can be monitored via MRI, as presently claimed. Thus, applicants respectfully submit that Unger '319 does not compensate for the deficiencies of Lang and/or Fenn and that claim 3 is patentably distinct from the combination of the cited art of record.

Regarding claims 9-11, applicants respectfully submit that Unger '319 does not disclose a method of monitoring the localization and distribution of a compound of

interest, e.g. drug release from an envirosensitive liposome, at a desired site and therefore does not compensate for the deficiencies of Lang and/or Fenn.

With respect to claims 35 and 37-40, applicants respectfully submit that the cited combination does not disclose a method of generating a heating profile of a site of interest. Thus, claims 35 and 37-40 are believed to be patentably distinct over the proposed cited combination.

Thus, applicants respectfully request that the rejection of claims 3, 9-11, 35 and 37-40 under 35 U.S.C. 103(a) be withdrawn. Applicants also respectfully request that the claims be allowed.

Response to the Rejection of Claims Under 35 U.S.C. § 103(a) Based on Lang in View of Fenn, Further in View of Unger '319 and Further in View of Unger et al. '935

Claims 14, 24, 32 and 36 stand rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lang in view of Fenn, further in view of Unger '319 and further in view of Unger et al. '935. As described above, the Patent Office asserts that Lang discloses a method of monitoring drug delivery to a tumor, comprising administering a non-sensitive liposome composition, wherein the liposome encapsulates a contrast agent and a therapeutic agent, and monitoring the accumulation of the compound of interest at the tumor site by MRI. Further, the Patent Office contends that Fenn teaches the use of a thermosensitive liposome and Unger '319 teaches the use of ultrasound to heat the tumor site. The Patent Office admits that none of these references described disclose a particular formulation of a

thermo-sensitive liposome. However, the Patent Office contends that Unger et al. '935 compensates for this deficiency by disclosing many different formulations of liposomes.

According to the contentions of the Patent Office Unger et al. '935 discloses many different formulations of liposomes, including DPPC-PEG. Therefore, the Patent Office contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use a thermosensitive liposome comprising a formulation of PEG and DPPC. The positions of the Patent Office as summarized above with respect to claims 14, 24, 32 and 36 are respectfully traversed as described below.

Applicants respectfully submit that the aforementioned discussion regarding the deficiencies of the methods disclosed by Lang, Fenn and Unger '319 are maintained in response to the current rejection.

Accordingly, applicants respectfully submit that Unger et al. '935 does not support the above-noted deficiencies in Lang, Fenn and Unger '319. Unger et al. '935 does not teach or suggest a method of monitoring drug delivery through the use of a thermosensitive liposome comprising a contrast agent and therapeutic wherein the accumulation of the liposome is monitored via MRI. Specifically, Unger et al. '935 does not disclose a thermosensitive liposome. Rather, Unger et al. '935 at best teaches what might be characterized as an ultrasound-sensitive liposome. See page 19, lines 7-23, and page 20, lines 34-37, of Unger et al. '935. Applicants respectfully submit that the disclosure of an ultrasound-sensitive liposome by Unger et al. '935 is

not tantamount to teaching a thermosensitive liposome. See page 11, lines 23-26 in the present U.S. patent application. Further, there appears to be no teaching in Unger et al. '935 of liposome formulations comprising DPPC-DSPE-PEG_{2000} or DPPC-MSPC-DSPE-PEG_{2000}.

Thus, applicants respectfully submit that Unger et al. '935 does not compensate for the deficiencies of the proposed cited combination. Applicants respectfully request that the rejection of claims 14, 24, 32 and 36 under 35 U.S.C. 103(a) be withdrawn. Applicants also respectfully request that the claims be allowed.

Response to the Rejection of Claims Under 35 U.S.C. § 103(a)

Based on Lang in view of Gamble et al.

Claims 5 and 21 stand rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lang in view of Gamble et al. As described above, the Patent Office asserts that Lang discloses a method of monitoring drug delivery to a tumor, comprising administering a non-sensitive liposome composition, wherein the liposome encapsulates a contrast agent and a therapeutic agent, and monitoring the accumulation of the compound of interest at the tumor site by MRI. The Patent Office admits that the reference lacks particular disclosure about the use of a liposome wherein the liposome DSPC/Cholesterol. However, the Patent Office contends that the teachings of the Gamble et al. compensate for this deficiency.

According to the contentions of the Patent Office Gamble et al. teach the use of a liposome comprising DSPC/Cholesterol. Therefore, the Patent Office contends

that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Gamble et al. with that of Lang. The positions of the Patent Office as summarized above with respect to claims 5 and 21 are respectfully traversed as described below.

Applicants respectfully submit that the aforementioned discussion regarding the deficiencies of the methods disclosed by Lang in monitoring the accumulation and distribution of a compound of interest *in vivo* is maintained in response to the current rejection.

Applicants respectfully submit that the teachings of Gamble et al. do not support the above-noted deficiencies in Lang. Specifically, Gamble et al. do not teach or suggest a method of monitoring the accumulation or distribution of a compound of interest at a desired site *in vivo,* wherein blood flow to the desired site is increased, as recited in claim 1. Since claim 5 depends from claim 1, and therefore shares the novel features of claim 1, claim 5 is believed to be patentably distinct over the combined teachings of Lang and Gamble et al.

Further, Gamble et al. do not provide a method of detecting an *in vivo* blood pool, as recited in claim 19. Since claim 21 depends from claim 19, and therefore shares the novel features of claim 19, claim 21 is believed to be patentably distinct over the combined teachings of Lang and Gamble et al.

Thus applicants respectfully submit that Gamble et al. do not compensate for the deficiencies of Lang. Applicants respectfully request that the rejection of claims 5

and 21 under 35 U.S.C. 103(a) be withdrawn. Applicants also respectfully request that the claims be allowed.

Discussion of New Claims

New claim 41 depends from claim 1 and recites the method set forth in claim 1, wherein the method is performed in real time. New claims 42-45 are independent claims reciting methods of monitoring the localization and distribution of a compound, detecting an *in vivo* blood pool, monitoring the accumulation of a compound and generating a heating profile, respectively, wherein the methods are performed in real time. Support for the addition of these new claims can be found at page 42, lines 25-33, and page 43, lines 1-2 of the present U.S. patent application, among other places.

The present methods can provide the ability to perform real time monitoring of events occurring *in vivo*. A researcher can monitor, for example, the accumulation of liposome compositions at a heated site as the accumulation is occurring, with the only delay associated with the obtaining and processing of images. This advantage is provided for, at least in part, through increased blood flow to the desired site.

The presently disclosed envirosensitive liposomes can also provide contrast enhancement, even at temperatures below their transition temperatures, as compared to non-envirosensitive liposomes. See Figures 1C and 1D of the instant U.S. patent application as filed. Also, as disclosed in the instant specification, the monitoring of the accumulating or localization and distribution of the compound of

interest can be accomplished in less than five minutes (see, for example, page 42, lines 24-30) and as little as 1 minute 45 seconds (see, for example, page 49, lines 18-19).

In marked contrast, the methods disclosed by Lang require substantially longer time periods for the monitoring disclosed therein. For example, tumor enhancement 5 minutes after Gd-labeled liposomes were injected provided only minimal enhancement of tumor tissue and tumor tissue enhancement, not believed to be statistically different from a pre-contrast image, and did not reach a maximum until 24 hours post injection. See page 12, lines 10-20, and Figure 1, of Lang. Accordingly, pre- and postcontrast images would be obtained with a time separation of 24 hours and thus could not be done within a single imaging session. See page 18, lines 3-5, of Lang.

Additionally, new claim 46 depends from claim 29. Claim 46 recites the method of claim 29, wherein there is increased blood flow to a desired site.

Further, the subject matter of claims 41-46 is not believed to be disclosed in any of the prior art documents of record. Accordingly, claims 41-46 are believed to be patentably distinguished over the cited art of record. Allowance of claims 41-46 is therefore respectfully requested.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: 04/23/2007 By: _____

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